Physicochemical Properties of β-Lactam Antibiotics: Oil–Water Distribution

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Abstract □ Apparent partition coefficients, P_{app}, of β-lactam antibiotics were determined in octanol–water and 2-methylpropanol–water systems at various pH values. The pKa values also were determined by potentiometry under the conditions of partition experiments. The intrinsic partition coefficients for the unionized form, P_u, and the ionized form, P_i, of β-lactam antibiotics were calculated from the equation $P_{app} = P_u[a_{H^+}/(K_a + a_{H^+})] + P_i[K_a/(K_a + a_{H^+})]$. The correlation between P_u and P_i values and lipophilic parameters of penicillins measured in other systems was examined.

Keyphrases □ Partition coefficients, apparent—various β-lactam antibiotics in octanol–water and 2-methylpropanol–water at various pH values □ pKa—various β-lactam antibiotics □ β-Lactam antibiotics—apparent partition coefficients in octanol–water and 2-methylpropanol–water at various pH values □ Antibiotics, various—apparent partition coefficients in octanol–water and 2-methylpropanol–water at various pH values

In biopharmaceutical studies of β-lactam antibiotics, the partition coefficient between two immiscible phases is an important physicochemical property for correlating their structure with their absorption, tissue distribution, renal reabsorption, and other membrane transport. Previously (1), the partition coefficient, k', determined by high-pressure liquid chromatography (HPLC) was reported for β-lactam antibiotics, and their log k' values were correlated with other reported partition properties such as log P (2) in octanol–water and R_m (2–4) determined by TLC.

Previously reported log P values for penicillins were determined either at only a single pH by a convenient flask-shaking method (5–7) or at one or two pH values by a pH-stat technique (2). Somewhat different partition properties from the previous data, however, were noted for several penicillins in this laboratory when particular attention was paid to the pKa, pH conditions, and their chemical instabilities.

This study investigated a series of β-lactam antibiotics; the results of pKa measurement, the apparent partition coefficient as a function of pH for determining the intrinsic P values for unionized and ionized species in octanol–water and 2-methylpropanol–water, and quantitative correlations among partition coefficients are discussed.

EXPERIMENTAL

Materials—All β-lactam antibiotics except methicillin and carbenicillin indanyl sodium (I) were described previously (1). Compound I[1] (704 μg/mg, containing 0.84% 5-indanol, 0.6% carbenicillin, and 1.4% penicillin G) and methicillin sodium[2] (853 μg/mg) were used as supplied. All other chemicals were analytical grade and were used without further purification, except that octanol was purified according to the literature (8) and 2-methylpropanol was used after a single distillation.

Determination of pKa—The apparent dissociation constant, K_a, for each penicillin was determined at 37° by a potentiometric titration (9). Twenty milliliters of 1.0×10^{-2} M solution of the sodium or potassium salt of penicillin, adjusted with potassium chloride to a constant ionic strength of 0.15, was titrated with 0.1 N HCl ($\mu = 0.15$ with potassium chloride) until precipitation of the penicillin free acid occurred.

The titrant was added in 0.2-ml portions from a buret[3], and the pH changes during titration were measured[4]. For acid-unstable penicillins such as penicillin G and methicillin, titrations were carried out as rapidly as possible to avoid the β-lactam cleavage. The apparent pKa values of penicillins were computed by the equation of Albert and Serjeant (9).

Determination of Apparent Partition Coefficient—For distribution experiments in octanol–water, the aqueous phase was prepared by dissolving an exactly weighed quantity of the sodium or potassium salt of the antibiotics to make a final concentration of 1×10^{-3} M and a calculated amount of potassium chloride to maintain a constant ionic strength of 0.15 in an appropriate buffer solution. To minimize the volume change due to mutual miscibility, the aqueous and organic phases were saturated previously with each solvent.

Exactly 10 ml of each solution (50 ml of organic phase was used for penicillin G, methicillin, and cephalothin) was transferred to a glass-stoppered flask and shaken for 2 hr (30 min for penicillin G and methicillin) to achieve complete equilibrium at 37 ± 0.1°. The two phases separated on standing for 1 hr, and the aqueous phase was centrifuged at 3000 rpm for 10 min. If necessary, after appropriate dilution with distilled water, the concentration of the antibiotics was determined by spectrophotometry[5] at 260 nm and/or by the imidazole method reported by Bundgaard and Ilver (10).

For the distribution study in 2-methylpropanol–water, each aqueous phase was prepared to make a constant Na^+ concentration of 0.1 M by the addition of a calculated amount of sodium chloride in buffer. Other procedures were the same as for the octanol–water system. Acetate, phosphate, and borate buffers were used in the distribution studies.

The apparent partition coefficient, P_{app}, was calculated from:

$$P_{app} = \frac{C_o V_w}{C_w V_o} \qquad \text{(Eq. 1a)}$$

$$P_{app} = \left(\frac{C_i - C_w}{C_w}\right)\frac{V_w}{V_o} \qquad \text{(Eq. 1b)}$$

where C and V represent the concentration and volume of the aqueous (subscript w) and organic (subscript o) phases, respectively, and C_i indicates the initial concentration of an antibiotic, which was determined by a simultaneous incubation of the antibiotic in the same buffer solution and for the same time as were used in the distribution experiment. In most cases, the suitable ratio, V_w/V_o, was used to maintain the condition of $1 < (C_i - C_w)/C_w < 10$.

RESULTS AND DISCUSSION

Dissociation Constants of Penicillins—Table I gives the apparent pKa values obtained as the average of a set of pKa values calculated at each pH measured during the titration, corresponding in most cases to 25–75% neutralization. In all cases, results from two or three titrations never deviated more than ±0.03 pKa unit.

Table I also lists similar results determined for some penicillins from titration in ethanol–water at 37°. For penicillin V and oxacillin, the pKa values extrapolated to 0% ethanol concentration in plots of the apparent pKa against the ethanol concentration [percent (weight per volume)] were in good agreement with the value determined directly in water. Therefore, the pKa values corresponding to those in water were obtained by extrapolation to 0% ethanol for the antibiotics unsuited to the usual de-

[1] Taito-Pfizer Co., Tokyo, Japan.
[2] Banyu Pharmaceutical Co., Tokyo.
[3] ABU12b autoburet, Radiometer, Copenhagen, Denmark.
[4] PHM26 pH meter, Radiometer, Copenhagen, Denmark.
[5] UV-200S double-beam spectrophotometer, Shimadzu, Kyoto, Japan.

Table I—Apparent Dissociation Constants of Penicillins in Water and Ethanol–Water Mixtures

Penicillin	pKa (This Research)[a] Temperature	Ethanol Concentration, w/v % 0.0	0.0[c]	16.0	32.8	41.9	51.4	pKa (Literature)[b] Temperature	Reported	Reference
I Carbenicillin indanyl sodium	37°	—	2.94	—	3.73	3.95	4.16	—		
II Carbenicillin phenyl sodium	37°	—	2.91	—	3.70	3.92	4.15	—		
III Dicloxacillin	37°	—	2.76	—	3.55	3.77	3.98	25°	2.67[c]	17
IV Floxacillin	37°	—	2.76	—	3.55	3.77	3.98	—		
V Cloxacillin	37°	—	2.78	3.11	3.57	3.79	4.01	25°	2.70, 2.73	11
								35°	2.68[d]	18
VI Oxacillin	37°	2.73	2.72	3.09	3.57	3.81	4.03	—		
VII Propicillin	37°	2.76	—	—	—	—	—	25°	2.72	11
VIII Phenethicillin	37°	2.80	—	—	—	—	—	25°	2.72, 2.74	11
								35°	2.9[d]	19
IX Penicillin V	37°	2.79	2.78	3.15	3.61	3.85	4.06	25°	2.73, 2.74	11
X Penicillin G	37°	2.75	—	—	—	—	—	25°	2.71, 2.73	11
								60°	2.78[d]	20
XI Methicillin	37°	2.77	—	—	—	—	—	25°	2.76, 2.78	11
								25°	2.74[d]	21

[a] The values were determined potentiometrically at $\mu = 0.15$. These values were computed from the equation of Albert and Serjeant (9) for the data corresponding to 25–75% of neutralization and averaged from at least three experiments, never deviating more than ±0.03 pKa unit. [b] The values were determined potentiometrically. [c] The pKa values were obtained by extrapolation to 0% (w/v) ethanol. [d] The values were determined at $\mu = 0.5$.

termination of the pKa in water because of their low solubility in aqueous acidic solution.

The pKa values in water determined directly or extrapolated at 37° and $\mu = 0.15$ were about 0.04 pKa unit higher than those determined at 25° by Rapson and Bird (11) for the corresponding penicillins (Table I). This difference may be due to different experimental conditions, temperature, and ionic strength, and it may be reasonable for the dissociation behavior of many carboxylic acids (9).

pH-Dependent Oil–Water Partition Behavior—If it is assumed that a certain β-lactam antibiotic, which is in the free acid and anionic forms at the dissociation equilibrium in water, is distributed between the oil and water phases as shown in Scheme I, then the apparent partition coefficient, P_{app}, can be expressed as:

$$P_{app} = \frac{(HA)_o + (A^-)_o}{(HA)_w + (A^-)_w} \quad \text{(Eq. 2)}$$

where (HA) and (A^-) represent the activities of the unionized and ionized forms, respectively, and the subscripts w and o indicate the water and oil phases, respectively. The true partition coefficient for unionized, P_u, and ionized, P_i, forms of an antibiotic and the dissociation constant, K_a, are given by Eqs. 3–5, respectively:

$$P_u = \frac{(HA)_o}{(HA)_w} \quad \text{(Eq. 3)}$$

$$P_i = \frac{(A^-)_o}{(A^-)_w} \quad \text{(Eq. 4)}$$

$$K_a = \frac{(A^-)_w a_{H^+}}{(HA)_w} \quad \text{(Eq. 5)}$$

Therefore, Eq. 6 can be derived from Eqs. 2–5:

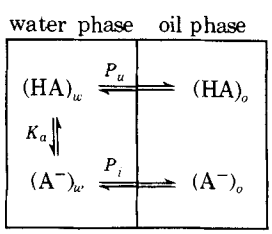
$$P_{app} = P_u\left(\frac{a_{H^+}}{K_a + a_{H^+}}\right) + P_i\left(\frac{K_a}{K_a + a_{H^+}}\right) \quad \text{(Eq. 6)}$$

where a_{H^+} is the hydrogen-ion activity. In these equations, the activity of the species in each phase is assumed to be approximately the same as its concentration. Rearrangement of Eq. 6 gives:

$$P_{app}\left(\frac{a_{H^+}}{K_a} + 1\right) = P_u\frac{a_{H^+}}{K_a} + P_i \quad \text{(Eq. 7)}$$

Equation 7 predicts that a plot of P_{app} ($a_{H^+}/K_a + 1$) against a_{H^+}/K_a should give a straight line with a slope of P_u and intercept of P_i.

Octanol–Water Distribution—The experimental results are summarized in Table II. All experimental conditions were selected for each antibiotic so that sufficient solubility in the aqueous phase could be achieved and that the β-lactam degradation was within 2% when the distribution equilibrium was attained. The degradation was checked in every case by simultaneous incubation of the antibiotic in the same buffer solution as that used for the distribution study.



Scheme I

Apparent partition coefficients of penicillin V were measured with various concentrations (5×10^{-4}–5×10^{-3} M) at a constant pH. No significant changes in P_{app} were observed (Table II), suggesting that no appreciable association between the molecules occurred in each phase. This result may be expected for other β-lactam antibiotics.

Figures 1 and 2 show the plots of $P_{app}(a_{H^+}/K_a + 1)$ *versus* a_{H^+}/K_a according to Eq. 7 for the data listed in Table II, where the K_a values used were those determined directly in water or extrapolated to 0% ethanol under the identical experimental conditions of 37° and $\mu = 0.15$ (Table I). For cephalothin, a pKa of 2.22, determined previously (12) at 35° and $\mu = 0.5$, was employed. The plots yielded straight lines for all β-lactam antibiotics studied and provided appreciable P_i values from the intercept only for antibiotics having log P_u values larger than about 2. These results suggest that the anionic species of β-lactam antibiotics also can be distributed depending on their side-chain lipophilicity.

Table III summarizes the log P_u and log P_i values for the octanol–water distribution. For comparison, previously reported values of log P_u for penicillins are listed in Table III. There are some close agreements and

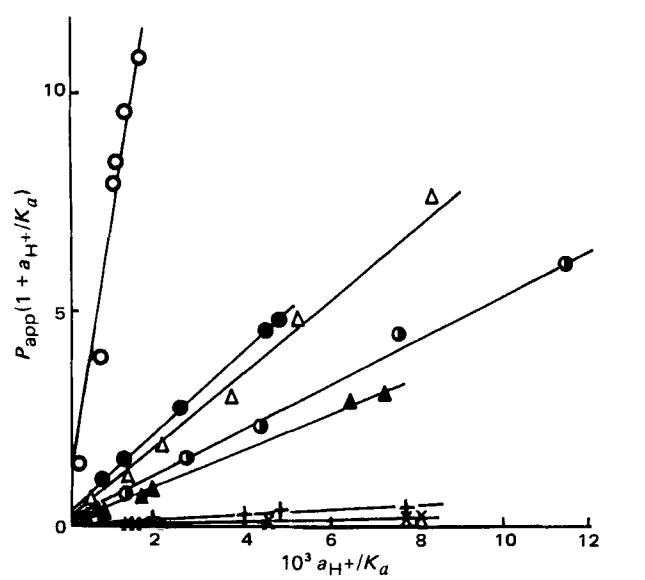


Figure 1—*Plots of* $P_{app}(1 + a_{H^+}/K_a)$ *against* a_{H^+}/K_a *for β-lactam antibiotics in octanol–water at 37° and* $\mu = 0.15$. *The compounds are numbered as in Table I. Key:* ○, *I;* ●, *II;* △, *III;* ▲, *IV;* ◑, *VII;* +, *X; and* ×, *XI.*

Table II—Apparent Partition Coefficient, P_{app}, of β-Lactam Antibiotics between Octanol and Water as a Function of the Aqueous Phase at 37° and $\mu = 0.15$

Compound	pH[a]	P_{app}[b]
I	5.73	10.80
	5.84	9.55
	5.92	8.39
	5.94	7.93
	6.55	3.89
	7.75	1.43
II	5.23	4.73
	5.26	4.47
	5.51	2.74
	5.84	1.54
	6.07	1.09
III	5.04	4.77
	5.19	2.96
	5.44	1.88
	5.65	1.17
	6.13	0.67
IV	4.90	3.07
	4.95	2.87
	5.49	0.87
	5.55	0.76
	5.90	0.41
	5.96	0.41
	6.22	0.27
V	4.26	8.08
	4.44	5.68
	4.77	3.04
	4.89	2.49
VI	4.15	7.21
	4.39	5.00
	4.83	2.13
VII	4.70	6.00
	4.88	4.39
	5.12	2.24
	5.35	1.55
	5.66	0.76
VIII	3.98	9.79
	4.06	7.88
	4.10	7.47
	5.21	0.76
IX	3.71	9.20
	4.05	4.56
	4.50	1.88
	4.93	0.66
	3.90	7.22[c]
	3.90	7.09
	3.91	6.77[d]
X	4.86	0.37
	5.07	0.32
	5.15	0.23
	5.47	0.15
XI	4.86	0.18
	4.88	0.14
	5.11	0.09
	5.61	0.02
	5.63	0.01
Cephalothin (XII)	3.13	0.97
	3.32	0.70
	3.55	0.39
	3.75	0.28
	3.77	0.27
	4.06	0.15
	4.40	0.08

[a] At equilibrium. [b] Initial concentration = 1×10^{-3} M. [c] Initial concentration = 5×10^{-4} M. [d] Initial concentration = 5×10^{-3} M.

some differences between the present values and those reported by Bird and Marshall (2), which were determined by the pH-stat titration method at pH 3 and 4 or only at pH 4. Unfortunately, since in that study there was no mention of the results available for recalculation and the temperature at which the partition coefficients were measured, it is difficult to evaluate the correlations between their values and the present ones.

2-Methylpropanol–Water Distribution—The apparent partition coefficients of several penicillins and cephalothin between 2-methylpropanol and aqueous buffer with a constant Na^+ concentration (0.1 M) are depicted in Fig. 3. The P_{app} values depended on the lipophilicity of the side chain for the penicillin series but were independent of pH above pH 6 for all β-lactam antibiotics, indicating the major contribution of the anionic forms for the P_{app} value. The average log P_i values are listed in Table III. In the pH–P_{app} profiles for penicillin V and propicillin, the increasing P_{app} with decreasing pH is undoubtedly attributed to the distribution of unionized forms.

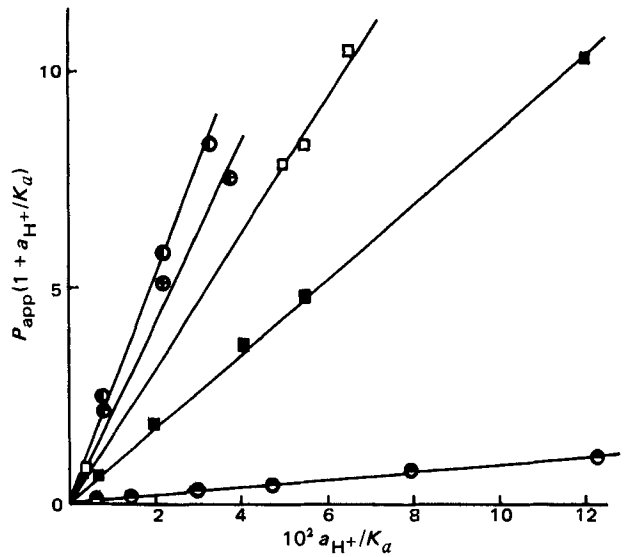


Figure 2—*Plots of* $P_{app}(1 + a_{H^+}/K_a)$ *against* a_{H^+}/K_a *for β-lactam antibiotics in octanol–water at 37° and* $\mu = 0.15$. *The compounds are numbered as in Table I. Key:* ◐, *V;* ⊕, *VI;* □, *VIII;* ■, *IX; and* ⊖, *XII.*

Scholtan (13) determined P_{app} values of penicillins in 2-methylpropanol–pH 7.4 phosphate buffer, and those values were 1.5–2 times larger than those in this work. Since Scholtan made no mention of experimental temperature conditions and the total buffer concentration, this large difference cannot be clarified. However, the partition coefficients of the penicillin anion in the present 2-methylpropanol–water system largely depend on the total Na^+ or K^+ concentration used for the buffer, and these phenomena also were observed in octanol–water (Table IV). Such behavior should be the result of a salting-out effect and/or ion-pair extraction of the penicillin anion with a buffer cation as suggested by Bird and Marshall (2).

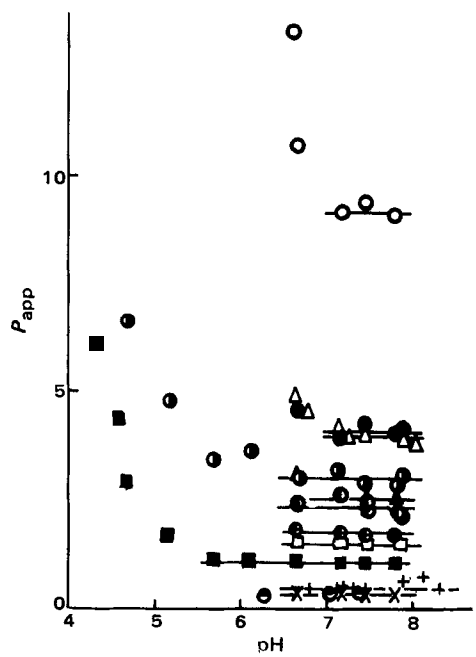


Figure 3—*Plots of* $P_{app}(1 + a_{H^+}/K_a)$ *against* a_{H^+}/K_a *for β-lactam antibiotics in 2-methylpropanol–water at 37° and constant* Na^+ *concentration (0.1 M). The compounds are numbered as in Table I. Key:* ○, *I;* ●, *II;* △, *III;* ▲, *IV;* ◐, *V;* ⊕, *VI;* ◑, *VII;* □, *VIII;* ■, *IX;* +, *X;* ×, *XI; and* ⊖, *XII.*

Table III—Partition Coefficients of β-Lactam Antibiotics

Compound	Octanol						Silicone			2-Methyl-propanol,	
	log P_u	log P_i	log P^a	log P^b	$R_m{}^a$ (pH 3)	$R_m{}^a$ (pH 4)	$R_m{}^c$ (pH 7.4)	$R_m{}^d$ (pH 2.6)	$R_m{}^d$ (pH 9.4)	log P_i	log k'^e
I	3.77	0.18	—	—	—	—	—	—	—	0.96	—
II	2.96	−0.52	—	—	—	—	—	—	—	0.62	2.68
III	2.91	−0.60	2.83	3.24	1.18	0.44	1.62	1.76	1.43	0.61	2.30
IV	2.61	−0.82	—	—	—	—	1.41[f]	—	—	0.41	2.14
V	2.43	—	2.44	2.49	0.71	0.01	1.34	1.67	1.21	0.38	2.04
VI	2.31	—	2.34	2.38	0.57	−0.15	1.05	1.39	0.96	0.25	—
VII	2.70	−0.70	2.58	—	0.97	0.21	—	—	—	0.48	—
VIII	2.20	—	2.19	2.20	0.50	−0.23	1.03	1.35	0.91	0.19	1.80
IX	1.95	−1.65[g]	2.01	2.03	0.34	−0.37	0.89	1.17	0.89	0.04	1.62
X	1.70	—	1.76	1.72	0.09	−0.66	0.55	0.84	0.45	−0.30	1.30
XI	1.30	—	1.13	1.06	−0.60	−1.34	0.47	0.78	0.41	−0.44	—
XII	0.95	—	—	—	—	—	—	—	—	—	—

[a] Reference 2. [b] Reference 7. [c] Reference 3. [d] Reference 15. [e] Reference 1. [f] Reference 14. [g] Evaluated from the data in Table IV.

Therefore, in the present experiment with 2-methylpropanol–water, the total Na^+ concentration was kept constant at 0.1 *M*. Thus, this effect would probably account for the greater discrepancy between the present data and those of Scholtan (13).

Linear Free Energy Relationship for Distribution Equilibrium of Penicillins in Various Systems—Since the partition coefficient is an equilibrium constant, there should be a linear free energy relationship between distribution values in different systems such as log *P* and R_m from the TLC method and log *k'* from the HPLC technique. The regression equations between two partition coefficients for penicillins determined in this study and available from the literature (1–6, 13–15) are given by Eqs. 8–21, where *n*, *r*, and *s* are the number of data, the correlation coefficient, and the standard deviation, respectively:

	n	*r*	*s*	
log P_u(octanol) = 0.994 log P_i(octanol) + 3.498	6	0.990	0.082	(Eq. 8)
log P_i(2-methylpropanol) = 0.598 log P_u(octanol) − 1.168	11	0.983	0.077	(Eq. 9)
log P_i(2-methylpropanol) = 0.510 log P_i(octanol) − 0.869	6	0.994	0.033	(Eq. 10)
R_m(octanol, pH 3.0) = 1.034 log P_u(octanol) − 1.791	8	0.984	0.080	(Eq. 11)
R_m(octanol, pH 4.0) = 1.034 log P_u(octanol) − 2.522	8	0.985	0.095	(Eq. 12)
R_m(silicone, pH 2.6) = 0.695 log P_u(octanol) − 0.190	7	0.963	0.102	(Eq. 13)
R_m(silicone, pH 7.4) = 0.775 log P_u(octanol) − 0.640	8	0.979	0.084	(Eq. 14)
R_m(silicone, pH 7.4) = 0.683 log P_i(octanol) + 2.009	3	0.996	0.036	(Eq. 15)
R_m(silicone, pH 7.4) = 1.116 log P_i(2-methylpropanol) + 0.887	8	0.985	0.071	(Eq. 16)
R_m(silicone, pH 9.4) = 0.682 log P_u(octanol) − 0.549	7	0.963	0.099	(Eq. 17)
R_m(silicone, pH 9.4) = 0.986 log P_i(2-methylpropanol) + 0.791	7	0.986	0.062	(Eq. 18)

Table IV—Effect of Na^+ or K^+ Concentration on Apparent Partition Coefficient (P_{app}) of Penicillin V in Octanol–Water and 2-Methylpropanol–Water Systems at 37°

Ionic Strength, *M*	Octanol–Water, with K^+	2-Methylpropanol–Water	
		K^+	Na^+
0.09	0.015	1.03	1.00
0.28	0.045	1.69	1.50
0.56	0.042	2.21	2.29

log *k'*(pH 7.4) = 0.936 log P_u(octanol) − 0.259	7	0.975	0.103	(Eq. 19)
log *k'*(pH 7.4) = 0.800 log P_i(octanol) + 2.903	4	0.942	0.146	(Eq. 20)
log *k'*(pH 7.4) = 1.327 log P_i(2-methylpropanol) + 1.163	7	0.961	0.125	(Eq. 21)

In the system with octanol as the organic phase, the slopes of these lines (Eqs. 8, 11, and 12) were close to 1.0, consistent with the theoretical expectation. The regression slope between log *P*(octanol) and log *k'* was near 1.0. This result probably means that the distribution process between the aqueous and stationary phases, octadecylsilane, is almost the same as that between water and octanol (16). A slope less than unity in the regression line was observed for the correlation between the octanol and 2-methylpropanol systems. The decreased lipophilic character of the nonaqueous phase decreases the energy required to transfer a distributing solute from the nonaqueous to the aqueous phase, which would result in a decrease of the slope going from octanol to 2-methylpropanol.

A good correlation between the partition coefficient for the unionized species and that of the ionized species of penicillin molecules was obtained in every partitioning system, indicating that the lipophilic character of the side chain of unionized penicillins is reflected in the lipoid solubility of the ionized forms. The present results suggest that the ionized form as well as the undissociated form of β-lactam antibiotics may be able to act in various processes *in vivo*, such as GI absorption, tissue distribution, serum binding, renal reabsorption, and cell wall permeability. Since penicillins and cephalosporins are almost all ionized at physiological pH, knowledge of the predominant species and the mechanism in these *in vivo* processes is important in the design of suitable β-lactam antibiotics and their dosage forms.

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Physiologically Based Pharmacokinetic Model for Digoxin Disposition in Dogs and Its Preliminary Application to Humans

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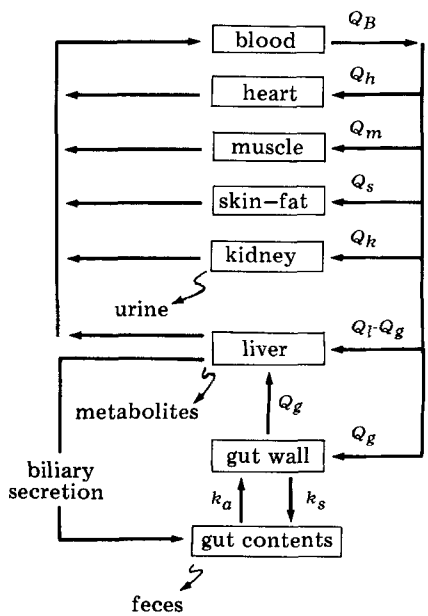
Abstract □ A physiologically based pharmacokinetic model for digoxin disposition developed in the rat was modified to account for the interspecies differences in tissue-to-plasma digoxin concentration ratios and applied to the dog. The model provided a quantitative assessment of the time course of digoxin concentrations in dog plasma, various tissues, and urine. It also predicted the effect of renal failure on digoxin pharmacokinetics in the dog. An attempt to scale the dog model to humans by simply considering differences in organ volumes, organ flow rates, and digoxin clearances was partially successful. Good predictions of plasma digoxin concentration and urinary digoxin excretion after a single dose and of steady-state plasma, heart, and skeletal muscle digoxin concentrations were obtained. However, the model predicted considerably higher kidney digoxin concentrations than are actually found. Although the model adequately characterized the time course of digoxin concentrations in patients with moderate renal impairment, it provided a relatively poor fit to that observed in anuric patients.

Keyphrases □ Digoxin—pharmacokinetic model for disposition in dog developed, applied to humans □ Pharmacokinetics—digoxin, model for disposition in dog developed, applied to humans □ Models, pharmacokinetic—for digoxin disposition in dog, developed, applied to humans □ Cardiotonic agents—digoxin, pharmacokinetic model for disposition in dog developed, applied to humans

Two- and three-compartment open models based on curve fits of plasma concentration–time data are commonly used to describe digoxin pharmacokinetics in humans and other species (1–4). Although these models are useful for clinical application, the basic information that they provide regarding distribution and elimination is intrinsically limited. Transfer rate constants calculated from such models have a high degree of uncertainty (5). Moreover, compartment volumes and transfer rate constants derived from these models have no anatomical or physiological reality. Neither the drug concentrations nor the time course of drug concentrations in particular target tissues other than the plasma can be predicted.

Recently, there has been an interest in the development of physiologically realistic pharmacokinetic models for drug disposition based on organ volumes and blood perfusion rates. In principle, these models permit the prediction of drug concentrations in any tissue at any time and may provide considerable insight to drug dynamics. Another useful feature of these models is that drug disposition in certain pathophysiological conditions may be simulated by altering estimates of organ blood flow (6, 7), drug clearance (8), or drug binding to tissues. Furthermore, under certain conditions, physiologically based models can be scaled to apply to more than one species (9). Therefore, for certain drugs, the large data base needed to develop a physiological pharmacokinetic model may be acquired in a laboratory animal and scaled to apply to humans. This approach has been used with several drugs (6, 10–13).

A detailed physiological model (Scheme I) recently was developed to describe digoxin pharmacokinetics in the rat



Scheme I